Anxiety Induced by Flooding Therapy for Phobias Does Not Elicit Prolactin Secretory Response*

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Eight subjects with severe phobias to insects and small animals had blood samples taken for measurement of prolactin concentration at regular intervals during five sessions of 3 hr duration each. Severe anxiety was induced by treating the phobia with *in vivo* flooding during the middle hour of the third and fourth sessions. Despite intense anxiety experienced by the subjects, they showed no change in plasma prolactin levels.

INTRODUCTION

Prolactin is a particularly interesting hormone to psychiatry because of its behavioral effects in many species (1), and because drugs which cause its release are often effective antipsychotic agents, presumably because prolactin inhibiting factor is controlled by dopaminergic neurones or is dopamine itself (2). There have been reports of prolactin secretion in response to various stimuli, including gastroscopy, sigmoidoscopy, intercourse (3), motion sickness (4), parachute jumping (5), and a mirror drawing task (6). A summary article states that "psychic factors alone, such as the anxieties connected with hospitalization and the anticipation of surgery, can raise prolactin levels in certain individuals" (7).

In view of these findings, we decided to use the severe anxiety caused by *in vivo* flooding treatment for phobias as a stimulus to test the hypothesis that prolactin secretion can be caused by anxiety alone.

Results of plasma cortisol and growth hormone levels obtained simultaneously on these subjects have been reported elsewhere. Anxiety-induced cortisol elevations were found in two of these subjects treated in the morning (8), but were absent in subjects treated in the evening (9). Five of these eight subjects showed some growth hormone response to anxiety (10). This article includes all subjects on whom complete prolactin data were obtained.

METHOD

Eight nonobese patients with severe phobias to insects, spiders, or small animals were recruited via classified advertisements. Medical history, physical exam, and blood count showed all subjects to be healthy. All the women had normal menstrual histories and none had recently used birth control pills. All subjects were medication free during the study. Their phobias were severe, with a rating of 4 or 5 on the Gelder and Marks phobia severity scale (11). This

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means the subjects all reported "strong fear" or "terror" at the presence of the object and "avoided the situation if at all possible."

The subjects were fully informed of the experimental design and gave their written consent. They were divided into morning and evening groups to control for diurnal variation of prolactin levels (12). There were three women and one man in each group. Morning subjects started at approximately 7 AM and evening subjects at 7 PM. The exact starting time for each subject was individually determined by adding 3 or 15 hr (for morning and evening subjects, respectively) to the average time of midsleep, which was calculated from a 2-week sleep record kept by each subject.

Each subject participated in five sessions, usually a week apart. Each session was 3 hr in duration. Sessions 1 and 2 were for laboratory adaptation, and session 5 was a control in which the subject sat quietly and read, except during the middle hour, when he or she was engaged in casual conversation to control for the presence of the therapist during the middle hour of the other sessions. Sessions 3 and 4 were similar except that *in vivo* flooding treatment for the phobia (13) was carried out during the middle hour. Subjects remained seated during this treatment hour, which consisted of confronting the patient with the actual object of his or her fear and encouraging him or her to get as close as possible, despite the anxiety, until the anxiety extinguished.

Blood samples were drawn every 20 min during each morning session and five times during each evening session (at times −60, 0, +20, +60, and +120 min, where 0 corresponds to the time of onset of flooding) via a 21-gauge butterfly needle, which remained in a forearm vein during the session. The butterfly tubing and stopcock were flushed with bacteriostatic saline after each blood sample was taken. Samples were centrifuged immediately, and the plasma was separated and frozen. Plasma prolactin concentrations [hPRL] were determined by a double antibody radioimmunoassay (14).

Subjects rated their anxiety level every 20 min during the experiment on a Subjective Units of Distress (SUD) scale which ranged from 0 ("no anxiety") to 100 ("the most anxious it is possible to feel").

If the phobia was not relieved by the 2 hr of treatment during these five sessions, the subject was offered additional treatment without blood sampling.

RESULTS

The mean SUD scores for all subjects are presented in Figure 1. Subjects were

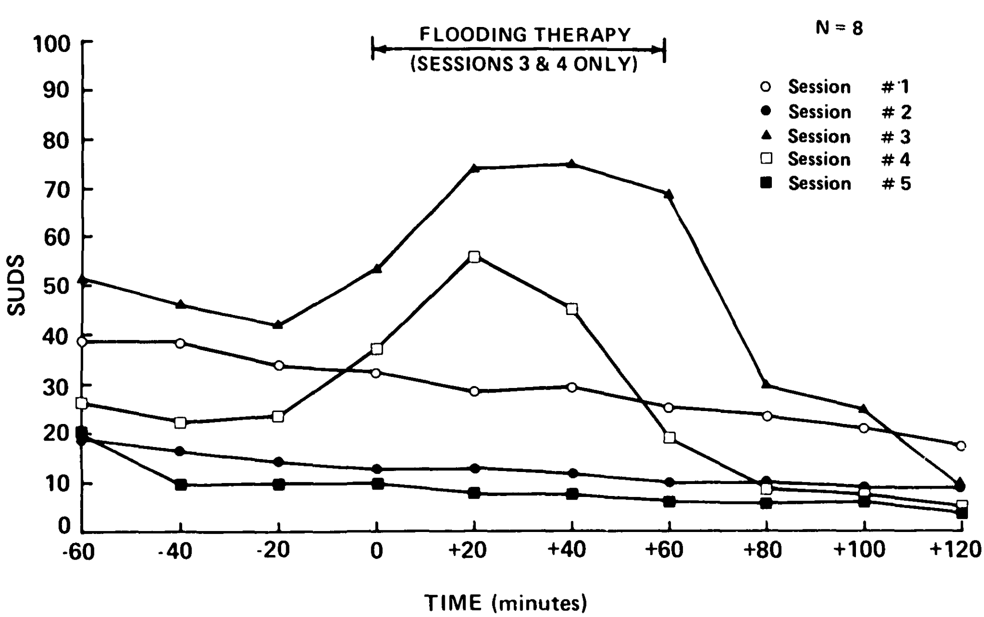

Fig. 1 Mean SUDS rating for all subjects.

generally calm except during session 1 and before and during flooding treatment in sessions 3 and 4. The intense arousal during treatment was indicated by signs such as tremors, gooseflesh, cold clammy skin, faltering voice, chattering teeth, screaming, and weeping. The subjects consistently reported that the peak anxiety they experienced during flooding treatment was as intense as any they had ever experienced.

Plasma prolactin data were analyzed separately for morning and evening subjects using a three-way Sessions × Subjects × Times analysis of variance (ANOVA) for repeated measures (Sessions and Times). Sessions and Times were treated as fixed effects and Subjects was treated as a random effect for the calculation of F ratios and interpretation of results (15).

Table 1 shows the ANOVA for the morning subjects. The sessions were not significantly different from each other. The differences between subjects were significant ($p < 0.001$) with [hPRL] means ranging from 12.5 to 24.1 ng/ml. The effect of time ($p < 0.001$) consisted of a steady decrease in [hPRL] during each session, from a mean of 24.0 ng/ml at $t = -60$ to 12.4 ng/ml at $t = +120$, which is consistent with expected diurnal variation (1).

The significant ($p < 0.01$) Sessions × Subjects interaction was accounted for by a high initial level (27.0 ng/ml) in session 2 for subject #2, which fell continuously during the session. No subject had higher levels during sessions 3 and 4, when flooding occurred, than in other sessions when it did not.

The significant ($p < 0.05$) Times × Sessions interaction is illustrated in Figure 2. The significance of the interaction appears to be due mainly to high levels during the first hour of sessions 2 and 5, which are hard to interpret. There was no trend towards a rise or fall of [hPRL] during the middle hours of sessions 3 and 4 when treatment occurred.

Results for the evening patients were similar, although the levels were lower because the samples were analyzed in a different laboratory. Identical samples sent to both laboratories were consistently 20–30% lower at the laboratory which ran the evening samples. Table 2 shows the ANOVA for the evening subjects. Sessions effect was not significant and there was no trend for sessions 3 or 4 to be different from the other Sessions. Subjects were again significant ($p < 0.01$) and the Times effect ($p < 0.01$) was again accounted for by a steady slow decrease during each session. Sessions × Times interaction was not significant.

TABLE 1. Prolactin Levels—Morning Subjects Analysis of Variance Summary

	Sum of Squares	*df*	Mean Square	*F*	*p*
Sessions	846.2	4	211.5	3.00	NS
Subjects	3701.6	3	1233.9	50.04	<0.001
Time	2235.0	9	248.3	10.00	<0.001
Sessions × Subjects	846.5	12	70.5	2.87	<0.01
Sessions × Time	1408.0	36	39.1	1.59	<0.05
Subjects × Time	670.0	27	24.8	1.01	NS
S × S × T	2658.8	108	24.6	—	—

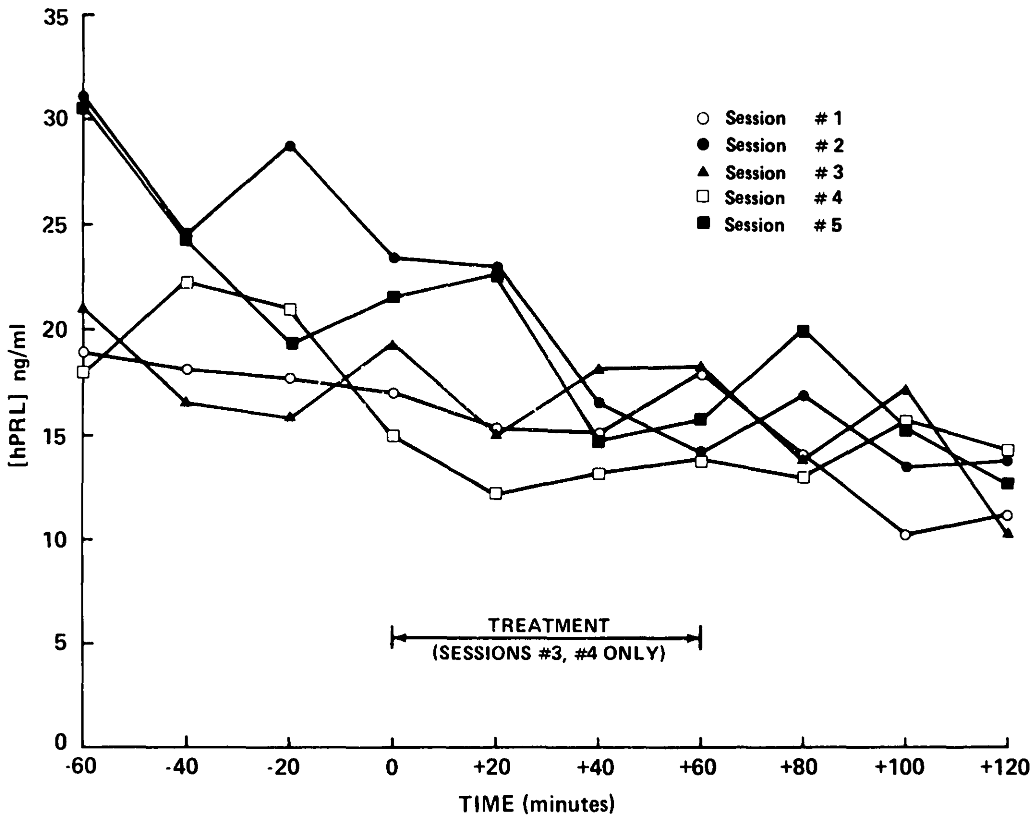

Fig. 2. Mean prolactin level of all morning subjects at each time in each session.

The significant ($p < 0.01$) Sessions by Subjects interaction was accounted for by a large rise in [hPRL] for subject 2 before treatment began in session 3 followed by a fall during treatment to ordinary levels. All other Subjects had [hPRL] levels during treatment sessions that were comparable to levels during the other sessions.

Figure 3 illustrates the Times × Sessions interaction where the rise before treatment during session 3 is again accounted for by a single patient.

Finally, visual review of graphs of each subject's individual prolactin levels confirmed that in no instance was there a marked change in [hPRL] during the treatment periods.

Clinical results of the phobia treatment were generally very good, and have been reported elsewhere (13).

DISCUSSION

Plasma prolactin levels are not changed by the intense anxiety caused by *in vivo* flooding therapy for phobias. This is a surprising result in view of reports of prolactin secretion in response to various stimuli. Noel et al. have shown prolactin response to surgery, gastroscopy, proctoscopy, exercise, and intercourse with orgasm (3). They note that no medication was given with the proctoscopy and that

TABLE 2. Prolactin Levels—Evening Subjects Analysis of Variance Summary

	Sum of Squares	*df*	Mean Square	*F*	*p*
Sessions	251.0	4	62.8	<1	NS
Subjects	446.8	3	148.7	12.82	<0.01
Times	434.4	9	48.3	4.61[a]	<0.01
Sessions × Subjects	1196.3	12	99.7	8.59	<0.01
Sessions × Times	374.8	36	10.4	<1	NS
Subjects × Times	159.1	27	5.9	<1	NS
S × S × T	1255	108	11.6	—	—

[a] Pooled variance of Subjects × Times and S × S × T is used as error term.

for surgical patients, preoperative levels of [hPRL] were three times the level in a control population. Miyabo et al. found a significant increase in prolactin following a frustrating "mirror drawing test" in which the subject traced an outline reflected in a mirror (6). This effect was present only for "neurotic females"; normal women and both normal and neurotic men did not show it. The stress of a first parachute jump caused a substantial increase in serum prolactin levels in young men (5), as did motion sickness induced by the Coriolis effect (4). Konincyx reported high and falling [hPRL] after pelvic examinations as evidence for stress hyperprolactinemia (16).

How can our results be understood in light of these other studies? Could we have missed secretory episodes? The

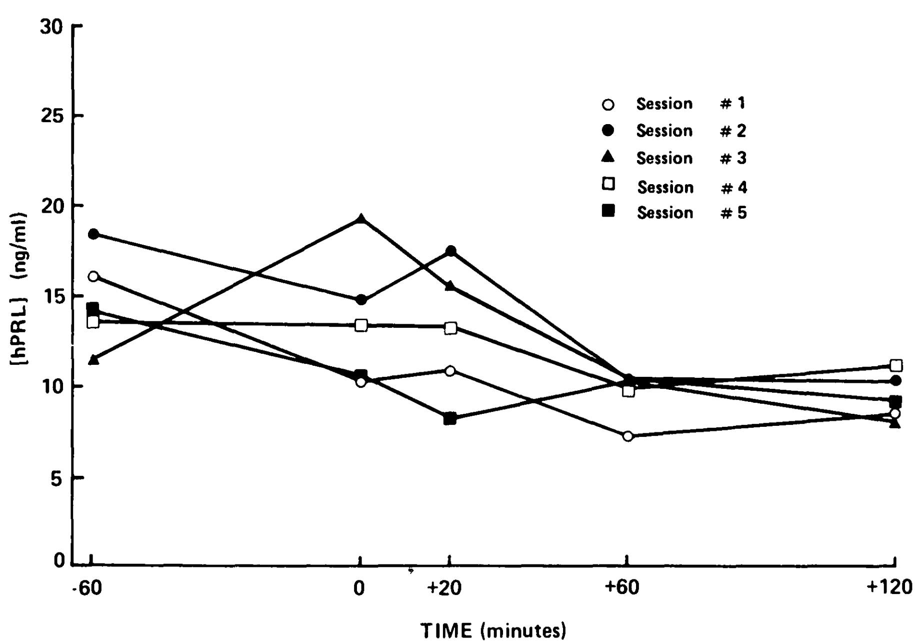

Fig. 3. Mean prolactin level of all evening subjects at each time during each session.

15–25 min half-life of circulating prolactin makes this unlikely, since we took samples every 20 min in one group of patients. Other details of our method, including medical screening, control periods before and after and on separate days, and performing the experiment at both extremes of the diurnal cycle, make it unlikely that we missed any significant changes in [hPRL].

Was our stimulus not intense enough? The levels of arousal, anxiety, and discomfort in this study were considerably greater than that of most other studies. Our subjects demonstrated their intense distress verbally, on a written scale, and by their behavior and autonomic arousal. In addition, many of them showed growth hormone or cortisol secretion in response to the treatment.

Could anticipation of the testing session itself have increased [hPRL] so that the system was already adapted to anxiety when flooding treatment began? This too seems unlikely, since the levels at the start of each session are not especially high and the slow decrease is consistent with diurnal variation.

The concept of stress as a nonspecific syndrome implies that any stressor should cause a stress response consisting of a uniform set of endocrine changes. In this study the anxiety was intense but there was no change in prolactin levels, despite previous demonstrated changes in growth hormone and cortisol in the same subjects. We suspect that endocrine responses to stressors are not general but are quite specific depending on the exact nature of the stressor. Our data support Mason's call for a re-evaluation of the concept of a nonspecific stress response (17).

SUMMARY

Previous research has suggested that "psychic factors alone," especially anxiety-provoking situations, can raise prolactin levels. We tested this hypothesis by exposing eight subjects to the intense anxiety associated with *in vivo* flooding therapy for severe phobias. Despite objective and subjective evidence that the subjects were intensely anxious, they showed no significant changes in prolactin levels. We conclude that severe anxiety of the type occurring during flooding therapy for phobias does not change prolactin levels, and we suggest that the idea of "stress" as a undifferentiated response needs to be reconsidered.

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